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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/679,581	DENNIS ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27-43,45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 27-43, 45 and 47-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 7 2009 has been entered.

Receipt of Amendments/Remarks filed on July 7 2009 is acknowledged. Claims 1-24, 26, 44 and 46 were/stand cancelled. Claims 25 and 45 were amended. Claim 48 was added. Claims 25, 27-43, 45 and 47-48 are pending.

Claim Objections

Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 38 depends from claim 25. Claim 25 is specifically directed to a microemulsion for intravenous delivery whereas claim 38 recites that the surfactant components are suitable for intravenous or oral administration. Therefore, the dependent claim is more broad than the claim from which is depends from.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 27-43, 45 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The specification, while being enabling for formation of a microemulsion comprising an oil phase and an aqueous phase wherein the oil-soluble drug is a liquid/oil at room temperature, does not reasonably provide enablement for formation of a microemulsion comprising oil phase and an aqueous phase wherein the oil soluble drug is a solid at room temperature. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. Specifically, the claims have been amended to recite that the oil phase does not comprise a carrier. However, the claims also recite that the composition is a microemulsion comprising an oil phase and an aqueous phase. Therefore, the specification does not provide enablement for formation of an oil phase when the oil-soluble drug is a solid.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Formal, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, relative skill level, and breadth of the claims

The instant invention is directed to a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug; a long chain

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is

polymer surfactant component; a short chain fatty acid surfactant component; wherein the oil phase is free of a carrier of the oil-soluble drug. The instant invention claims a composition comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug; and an emulsifier combination comprising a long chain polymer surfactant and a short chain fatty acid surfactant wherein the emulsifier combination is free of a carrier of the oil-soluble drug.

The relative skill of those in the art is high, that of an MD or PHD.

The state and predictability of the art

While there is predictability in forming a microemulsion from an oil and aqueous phase. The instant claims specifically recite that the composition comprises an oil phase and an aqueous phase wherein the oil phase is free of a carrier of the oil-soluble drug. When the drug is an oil/liquid at room temperature then this serves as the "oil" portion of the oil microemulsion. However, if the drug is a solid then how is there an oil phase. The instant claims recite that the composition comprises any oil-soluble drug. Specific examples in the specification include aspirin, acetaminophen, ibuprofen, lidocaine and thiobarbiturates. The Merck Index teaches that aspirin (page 134), acetaminophen (page 8), ibuprofen (page 776) and lidocaine (page 863) are all solids. Feld (US Patent No. 5274093) teaches that thiobarbiturate is a solid (examples).

The lack of significant guidance from the specification or the prior art with regard to formation of a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase is free of a carrier of the oil-soluble drug utilizing any oil-soluble drug

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"undue", not "experimentation".

makes practicing the scope of the invention unpredictable.

The amount of direction or guidance provided and the presence or absence of working examples and The quantity of experimentation necessary

The specification provides no direction or guidance for formation of an oil phase wherein the oil-soluble drug is a solid. Due to the vastness of compounds classified as oil-soluble drug, one of ordinary skill would undergo undue experimentation in determining how to formulate a microemulsion comprising an oil phase without an oil carrier when the oil-soluble drug is a solid.

The working examples of the specification are directed towards formation of a microemulsion comprising propofol, surfactants and saline. However, the examples do not enable one to utilize any oil-soluble drugs to form a microemulsion comprising an oil phase and an aqueous phase.

Conclusions

Because of the specification does not teach how to form a microemulsion with an oil phase and aqueous phase wherein the oil phase is free of a carrier when the oil-soluble drug is a solid, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to form a microemulsion comprising an aqueous phase and oil phase wherein the oil phase is free of a carrier as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no

assurance of success.

Claims 25, 27-43, 45 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25 and 45 introduce new matter as the claims recite the limitation: "free of a carrier of the oil-soluble drug" There is no support in the specification for this limitation. The limitation of: "free of a carrier of the oil-soluble drug" was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. Applicants have indicated support from the amendment comes from the example. While the example provides support for the specific composition exemplified, it does not provide support for formation of any microemulsion comprising an oil phase and an aqueous phase wherein the oil phase or surfactant combination is free of a carrier for the oil phase. The instant specification provides no definition for the term carrier. Therefore, the instant specification provides no guidance as to what components are contemplated as being excluded from the oil phase. The specification discloses an oil phase consisting of propofol, Pluronic F-77, sodium laurate but does not describe the instantly claimed limitation. Therefore, it is the Examiner's position that the

disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 27-30, 34, 37-38, 40-41, 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (US Patent No. 6024978, cited in the Office action mailed on 6/12/08) as evidenced by The Merck Index (1989, cited in the Office action mailed on 6/12/08).

Applicant Claims

The instant application claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug, a long chain polymer surfactant and a short chain fatty acid surfactant wherein the oil phase is free of a carrier of the oil-soluble drug. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1 μm or 100 to 1000 angstroms).

The instant application claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug; and an emulsifier combination comprising a long chain polymer surfactant and a short chain fatty acid surfactant wherein the emulsifier combination is free of a carrier of the oil-soluble drug. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1 μm or 100 to 1000 angstroms).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Hauer et al. is directed to pharmaceutical formulations comprising cyclosporin. Ciclosporin is disclosed as a very hydrophobic compound (column 3, line 26). The

microemulsions comprise a hydrophilic phase, a lipophilic phase and a surfactant along with cyclosporin. Cyclosporin is present in an amount from 1 to about 30% (column 17, lines 12). Example 5.2 (column 30) is directed to a thickened emulsion pre-concentrate type comprising cyclosporin, Pluronic F68 and sodium laurylsulphate. Pluronic F68 is disclosed by applicant (page 15 of the specification) as a suitable long chain polymer surfactant. Hauer et al. disclose that microemulsions obtained from the microemulsion pre-concentrates having an average particle (droplet) size of less than 1500 angstroms preferably less than 1000 angstroms and down to about 150 or 200 angstroms. It is disclosed that the microemulsions of Hauer et al. enable effective cyclosporin dosing with concomitant enhancement of resportion/bioavailability as well as reduced variability in individual patients (column 5, line 3-4). Dosage types of the formulation include topical and oral dosage forms (abstract). It is disclosed in addition to cyclosporin that the composition may include one or more further ingredients such as alpha-tocopherol. The use of a tocopherol is disclosed as being particular advantageous (column 13, lines 35-41).

The Merck Index indicates that sodium lauryl sulfate contains 12 carbons thereby fitting applicant's definition of a short chain fatty acid surfactant.

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

Hauer et al. do not exemplify a microemulsion with Pluronic F68 and sodium laurylsulfate. Hauer et al. do not exemplify a microemulsion comprising cyclosporin and

alpha-tocopherol. However, Hauer et al. do exemplify an emulsion with these surfactants and indicate that the addition of alpha-tocopherol is preferable.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to formulate example 5.2 as a microemulsion. One of ordinary skill in the art would have been motivated to formulate a microemulsion of this type as the surfactants, Pluronic F68 and sodium laurylsulphate are disclosed as being suitable surfactants and are exemplified in an emulsion type formulation. One of ordinary skill in the art would have been motivated to choose these surfactants from those listed as suitable because Hauer et al. exemplify utilizing these surfactants in combination.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to further add alpha-tocopherol (vitamin E) to the microemulsion. One of ordinary skill in the art would have been motivated to add tocopherol as it is disclosed by Hauer et al. as being suitable and advantageous.

Regarding instant claim 43, Hauer et al. disclosed that the microemulsions enable effective cyclosporin dosing with concomitant enhancement of resportion/bioavailability as well as reduced variability in individual patients. Therefore, it is the microemulsion that is controlling the drug transfer rate.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 31-33, 39, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. in view of Constantinides et al. (WO 9408610, cited on PTO Form 1449).

Applicant Claims

The instant application claims that the long chain polymer surfactant component is a poloxamer and the short chain fatty acid surfactant component is a laurate. Applicant claims that the interfacial tension is less than 0.1 dynes per cm. Applicant claims that the total amount of both surfactants does not exceed 4.65%. Applicant claims that the ratio of long chain to short chain surfactant is from 10:100 to 25:80 wt/wt.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Hauer et al. are set forth above. Specifically Hauer et al. disclose microemulsions. Surfactants exemplified include a poloxamer, Pluronic F68, and sodium laurylsulphate.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Hauer et al. do not specify that the surfactant can be a laurate. Hauer et al. do not specify the amount of the surfactants are less than 4.65% or that the ratio of long to short chain surfactant is from 10:100 to 25:80 wt/wt. Hauer et al. do not specify the interfacial surface tension. However, these deficiencies are cured by Constantinides et al.

Constantinides et al. is directed to microemulsions comprising an oil, a mixture of high and low HLB surfactants (abstract). It is disclosed that it has been long recognized

that low interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than $2x10^{-2}$ dyn/cm results in stable microemulsions (page 1, lines 23-28). It is disclosed that the incorporation of medium-chain fatty acid salts have been found to further enhance the absorption of a biologically active agent (page 5, lines 29-30). Medium chain is defined as fatty acyl chain having from 6 to 12 carbon atoms (page 5, lines 36-37). A particular combination of high HLB surfactant combination exemplified is Tween 80 and sodium laurate (example 7). It is disclosed that high HLB surfactants such as the medium chain fatty acids and Tween 80 (which is indicated by Applicant as being a suitable long chain fatty acid surfactant (page 16 of the specification)) are present in an amount from about 5 to about 75% (page 15, lines 5-7). Constantinides et al. indicates that one of skill in the art would know that in order to accommodate a larger amount of a hydrophilic phase then this will have be matched by an increase in the relative amount of high HLB surfactant (page 15, lines 13-16).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hauer et al. and Constantinides et al. and utilize sodium laurate in combination with another high HLB surfactant such as Tween 80 or Pluronic F68. One of ordinary skill in the art would have been motivated to utilize sodium laurate in combination with another high HLB surfactant as medium chain fatty

acid salts have been found to further enhance the absorption of biologically active agents as taught by Constantinides et al.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to optimize the amount and ratio of the high HLB surfactants present in the microemulsion. One of ordinary skill in the art would have been motivated to optimize the amount and ratio depending on the surfactants utilized as the well as the amount of a hydrophilic phase. Constantinides et al. indicates that a larger amount of a hydrophilic phase results in a higher requirement of a high HLB surfactant needed, therefore, the smaller the hydrophilic phase the less high HLB surfactant is needed. Therefore, the amount and ratio of surfactants in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

Regarding the interfacial tension, Hauer et al. is silent as to the interfacial tension. Constantinides et al. disclosed that it has been long recognized that low

interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than $2x10^{-2}$ dyn/cm results in stable microemulsions (page 1, lines 23-28). Therefore, when desiring a stabile microemulsion it would have been obvious to one of ordinary skill in the art to select surfactants that exhibit low solubility in both oil and water phases as taught by Constantinides et al.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 35-36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. as evidenced by The Merck Index (1989, page 1364, cited in the Office action mailed on 6/12/08) in view of The Merck Index (1989, page 478, cited in the Office action mailed on 6/12/08).

Applicant Claims

The instant application claims that the drug is an anesthetic. Applicant claims that the drug is an aryl containing molecule. The instant application claims that the drug is a mixture of the base form and the salt form of the drug. The instant application claims that the microemulsion comprises at least two oil-soluble drugs.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Hauer et al. are set forth above. Hauer et al. is to the delivery of cyclosporin via a microemulsion. It is disclosed that Ciclosporin is applicable to a variety of inflammatory conditions such as arthritis (column 1, lines 61-63).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Hauer et al. do not specify that anesthetic or aryl containing molecules can be included in the microemulsion. Hauer et al. do not specify that the drug is a mixture of the base form and the salt form of the drug. However, this deficiency is cured by The Merck Index.

The Merck Index indicates that dibucaine which is a local anesthetic is available as the hydrochloride salt as well the base form. The structure of dibucaine contains an aryl group.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hauer et al and The Merck Index and utilize dibucaine in the microemulsion. One of ordinary skill in the art would have been motivated to add dibucaine because it is taught by Hauer et al. that ciclosporin is used to treat inflammatory conditions such as arthritis. Therefore, the incorporation of an anesthetic would have an additive effect in treating the symptoms of the condition sought to be treated by Hauer et al.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize both the base form and salt form of the anesthetic. One of ordinary skill in the art would have been motivated to utilize this form because both forms are known and the incorporation of both forms would allow for the increased solubility of the drug as the base form would be more oil soluble while the salt form would be more water soluble.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that the example pointed to by the examiner (example 5.2) includes transcutol. It is argued that transcutol is taught as a component of the lipophilic phase. Applicants specifically point to column 7, lines 14-50 for providing support.

Applicants' arguments filed July 7 2009 have been fully considered but they are not persuasive.

Firstly, the section pointed to by applicants is specifically directed to components of the hydrophilic phase. Secondly, the abstract clearly states that Transcutol is a hydrophilic component. Since, the instant application recites the open claim language of comprising; the current claim language does not exclude Transcutol from being present in the hydrophilic phase (i.e. aqueous phase).

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Claims 25, 27-41, 43, 45 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glen et al. (US Patent No. 4798846) in view of Constantinides et al.

Applicant Claims

The instant application claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug, a long chain polymer surfactant and a short chain fatty acid surfactant wherein the oil phase is free of a carrier of the oil-soluble drug. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1 μm or 100 to 1000 angstroms).

The instant application claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug; and an emulsifier combination comprising a long chain polymer surfactant and a short chain fatty acid surfactant wherein the emulsifier combination is free of a carrier of the oil-soluble drug. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1 μm or 100 to 1000 angstroms).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Glen et al. is directed to pharmaceutical compositions. The invention relates to pharmaceutical compositions which may be administered parenterally to a warm-

blooded animal for the production of general anesthesia (column 1, lines, 7-10). One embodiment is a composition which is an oil in water emulsion in which the 2,6-diisoproopylphenol either alone or dissolved in a water-immiscible solvent and is emulsified with water by means of a surfactant (column 1, lines 53-59). Examples of surfactants include ethoxylated fatty acids, those derived from polyethoxylated sorbitan and a fatty acid such as Tween, polyoxyethylene-polyoxypropylene block copolymers such as Pluronics (aka poloxamers). Specific surfactants taught include Tween 20, 40, 60, 80, Cremophor, and Pluronic F68 (columns 1-2, lines 60-68 and 1-20). The amount of surfactant ranges from 2 to 30% by weight of the composition and 0.1 to 5% by weight of 2,6-diisopropylphenol (column 2, lines 46-50). The composition may optionally contain one or more additional constituents such as stabilisers, preservatives or antioxidants (column 2, lines 66-68). The compound, 2,6-diisopropylphenol, produces smooth and rapid anesthesia when injected intravenously as a composition of the invention (column 3, lines 40-42). Exemplified surfactants include, Tween 20, 40, 60, 80 and Pluronic F68. The examples are taught as being micro-emulsions. It is specifically taught that the resulting emulsion is repeatedly passed through a homogeniser until a suitably low particle size is formed (example 7).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Glen et al. teach the form of the composition can be that of a micro-emulsion and that passage through a homogeniser until a suitably low particle size is formed, Glen et al. does not specify the particle size of the micro-emulsion. While Glen et al. teach the composition can comprise an antioxidant, Glen et al. does not specify

the incorporation of tocopherol. However, these deficiencies are cured by Constantinides et al.

Constantinides is directed to microemulsions comprising an oil, a mixture of high and low HLB surfactants (abstract). It is disclosed that it has been long recognized that low interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than $2x10^{-2}$ dyn/cm results in stable microemulsions (page 1, lines 23-28). It is taught that there are many advantages to the use of a microemulsion over conventional emulsions for drug transport. Microemulsions form spontaneously, without the need for a high input of energy and therefore easy to prepare and scale up for commercial applications. They have thermodynamic stability due to their small particle size and therefore have a long shelf life; they have an isotropically clear appearance so that they may be monitored by spectroscopic means; they have relatively low viscosity and are therefore easy to mix. (page 2, lines 9-22). It is disclosed that the incorporation of medium-chain fatty acid salts have been found to further enhance the absorption of a biologically active agent (page 5, lines 29-30). Medium chain is defined as fatty acyl chain having from 6 to 12 carbon atoms (page 5, lines 36-37). A particular combination of high HLB surfactant combination exemplified is Tween 80 and sodium laurate (example 7). It is disclosed that high HLB surfactants such as the medium chain fatty acids and Tween 80 (which is indicated by Applicant as being a suitable long chain fatty acid surfactant (page 16 of

the specification)) are present in an amount from about 5 to about 75% (page 15, lines 5-7). Constantinides indicates that one of skill in the art would know that in order to accommodate a larger amount of a hydrophilic phase then this will have be matched by an increase in the relative amount of high HLB surfactant (page 15, lines 13-16). The diameter of droplets or particles of the microemulsions are less than 150 nm, preferably less than 100 nm, and most preferably in the range of 5 to 35 nm (page 16, lines 8-11). The compositions can comprise optional ingredients such as antioxidants such as tocopherol (page 16, lines 18-20).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and utilize sodium laurate in combination with another high HLB surfactant such as Tween 80 or Pluronic F68. One of ordinary skill in the art would have been motivated to utilize sodium laurate in combination with another high HLB surfactant as medium chain fatty acid salts have been found to further enhance the absorption of biologically active agents as taught by Constantinides et al.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and to optimize the amount and ratio of the high HLB surfactants present in the microemulsion. One of ordinary skill in the art would have been motivated to optimize the amount and ratio depending on the surfactants utilized as the well as the amount of a hydrophilic phase. Constantinides et al. indicate that a larger amount of a hydrophilic phase results

in a higher requirement of a high HLB surfactant needed, therefore, the smaller the hydrophilic phase the less high HLB surfactant is needed. Therefore, the amount and ratio of surfactants in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and utilize a droplets or particles of the microemulsions less than 150 nm. One of ordinary skill in the art would have been motivated to utilize a microemulsion as Glen et al. teach and exemplify microemulsion formulations and Constantinides et al. teach that microemulsions have many advantages over conventional emulsions such as they form spontaneously and therefore are easy to prepare and scale up. Therefore, one of ordinary skill in the art would have been motivated to formulate a microemulsion due to

their many advantages and utilize a particle size of less than 150 nm, which is a taught particle size of a microemulsion, based on the teachings of Constantinides et al.

Regarding the claimed long chain polymer surfactant component, Pluronic F68 (page 15 of the specification) and Tween 80 (page 16 of the specification)) are taught as a suitable long chain polymer surfactant.

Regarding the interfacial tension, Glen et al. is silent as to the interfacial tension. Constantinides disclosed that it has been long recognized that low interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than $2x10^{-2}$ dyn/cm results in stable microemulsions (page 1, lines 23-28). Therefore, when desiring a stabile microemulsion it would have been obvious to one of ordinary skill in the art to select surfactants that exhibit low solubility in both oil and water phases as taught by Constantinides.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and add the antioxidant tocopherol to the microemulsion. One of ordinary skill in the art would have been motivated to add tocopherol as Glen et al. teach that the composition can include antioxidants as Constantinides et al. teach that antioxidants known include tocopherol. Therefore, it would have been obvious to one of ordinary skill in the art to add tocopherol for it's antioxidant effect.

Regarding claim 47, since it would have been obvious to add tocopherol, the addition of tocopherol results in a composition comprising two oil soluble drugs (tocopherol and propofol).

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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